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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/796,861	03/08/2004	Paul Calabresi	21486-031CON2	2424

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EXAMINER	
HAGHIGHATIAN, MINA	
ART UNIT	**PAPER NUMBER**
1616	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/796,861	CALABRESI ET AL.	
	Examiner	Art Unit	
	Mina Haghighatian	1616	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *05 January 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-8,10-20 and 22-24* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-8, 10-20 and 22-24* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Receipt is acknowledged of the Amendments and Remarks filed on 01/05/07. Claims 1-8, 13-20 have been amended while claims 9, 21 and 25-77 have been cancelled. Accordingly, claims **1-8, 10-20 and 22-24** are pending.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 1-3, 5, 7-8, 10-15, 17, 19-20 and 22-24 are rejected under 35 U.S.C. 102(e) as being anticipated by Stendel et al (6,479,481).

Stendel et al teach methods and compositions for treating **primary and secondary** tumors of the central nervous system. The agents used in the said treatments are metholyl transfer agents including taurolidine and/or taurultam (see col. 3, lines 23-45). The treatment of CNS tumors may include glioblastoma multiforme, **recurrent** malignant gliomas, high grade gliomas, **recurrent** high grade primary brain tumors, etc (see col. 4, lines 10-29). Taurolidine and/or tauraltam may be administered

by injection or infusion or by local application. It is also disclosed that separately or simultaneously with administration of a methylol transfer agent in accordance with the said treatment, other agents can be administered to the patient, including cytotoxic, antineoplastic agents(including alkylating agents and/or agents involved in tumor metabolism) (see col. 8, lines 1-29).

Claim Rejections - 35 USC § 103

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claims 1-2, 5, 10-14, 17-20 and 22-24 are rejected under 35 U.S.C. 103(a) as being unpatentable over Pfirrmann et al (5,593,665) in view of Morrissey et al (WO 9852572).

Pfirrmann teaches products containing tumor necrosis factor (TNF), and taurolidine and/or taurultam as a combined preparation for simultaneous, separate or sequential use for treatment of patients suffering from medical conditions mediated by TNF (see abstract). Pfirrmann discloses that the antibacterial compounds taurolidine and taurultam are significantly effective in reducing the toxicity and side effects of TNF. The findings show that taurolidine and taurultam do not inhibit the anti-tumor effect of TNF, but, in fact, augment such cytotoxicity. Also taurolidine and taurultam do not have

significant cytotoxic effects against normal cells and may thus be safely used in combination with TNF in combating tumors (col. 1, line 58 to col. 2, line 45).

Pfirrmann teaches that other agents known to be involved in tumor metabolism may also advantageously be co-administered in conjunction with the said therapy. Such agents include gamma-interferon, interlukin-1, and interlukin-2, cytotoxic agents such as adriamycine and actinomycine (col. 2, 46-51). Pfirrmann lacks teachings on the methods of treating tumors.

Morrissey teaches the use of taurolidine for treatment of leukemia through the induction of apoptosis in leukemia cells. Taurolidine is administered by injection in solution to afflicted patients in an amount effective to cause apoptosis of monocytic and/or myeloid cells. The cells involved in the monocytic or myeloid leukemia disease are thus attacked and die via **apoptosis** (page 12 lines 1-8).

Morrissey teaches the effects of taurolidine on cell viability and growth rates, where apoptosis is a controlled form of cell death characterized by the fact that neither parent cells nor apoptotic bodies become membrane-permeable. Also it was found that taurolidine causes apoptosis rather than necrosis of leukemia cells (page 22, lines 4-11).

It would have been obvious to a person of ordinary skill at the time the invention was made to have modified the teachings of Pfirrmann on the use of taurolidine and taurultam in treating tumors, by adding the method of treatments as taught by

Morrissey, because of the expectations of treating patients in need of such treatments with the most effective medications and the least possible amount of side effects. In other words the combination of Pfirrmann et al and Morrissey et al provide sufficient information to one of ordinary skill in the art to make and use the invention as claimed.

Claims 3-4, 6-8 and 15-16 are rejected under 35 U.S.C. 103(a) as being unpatentable over Pfirrmann et al (5,593,665) in view of Morrissey et al (WO 9852572) as applied to claims 1-2, 5, 10-14, 17-20 and 22-24 above, and further in view of Samid (5,661,179).

Pfirrmann and Morrissey were discussed above. The combined references lack specific teachings on treating the various types of tumors.

Samid teaches methods for treating neoplastic conditions using phenylacetic acid and a method of treating a method of monitoring the bioavailability of a compound for treatment of a pathology not associated with hemoglobin. The method comprises administering to a subject the compound and measuring the level of hemoglobin TGF-beta 2, IL-6 or TGF –alpha. Also disclosed is method of treating neoplastic condition in cells resistant to radiation and chemotherapy, specifically, the multiple drug resistant cells (col. 3, lines 34-42).

Samid teaches methods of treating malignant conditions such as prostatic cancer, melanoma, brain tumors, glioma, astrocytoma, Kaposi's sarcoma, lung adenocarcinoma, leukemia, myelodisplasia, etc (col. 7, lines 29-43).

It would have been obvious to a person of ordinary skill at the time the invention was made to have modified the combined teachings of Pfirrmann and Morrissey by substituting phenylacetate of Samid with taurolidine and/or taurultam, with a reasonable expectations of successfully producing compositions and methods of treatment for various tumors. Although non of the applied references specifically disclose treating ovarian cancers, they recite a broad disclosure of treating tumors and Samid discloses treating malignant conditions.

Claims 1-8, 10-20 and 22-24 are rejected under 35 U.S.C. 103(a) as being unpatentable over Monson (WO 9200743).

Monson teaches methods of treatment or prophylaxis of tumors in mammalian subjects wherein an effective dose of taurolidine and/or taurultam is administered to a mammalian subject suffering from or at risk of tumor growth (page 1, lines 18-22).

Monson discloses that taurolidine and taurultam may be administered systemically, i.e. by injection or infusion, or by direct application, e.g. topically, to external tumors. Suitable formulation for injection or infusion may comprise an isotonic

solution containing one or more solubilising agents in order to provide solutions of increased taurolidine or taurultam concentration (page 2, 2nd and 3rd paragraphs).

Monson teaches that other agents known to be involved in tumor metabolism may also advantageously be co-administered in conjunction with the said formulation. Such agents include interlukins, gamma-interferon, etc. Cytotoxic agents such as adriamycin and actinomycin D may be co-administered. The tumors to be treated may be of any type, including lymphomas, sarcomas, melanomas and carcinomas. It is particularly beneficial to use taurolidine and/or taurultam prevent the spread of metastases, especially following surgical removal of tumors. The mammalian subjects are typically humans (page 3, lines 1-23).

Although Monson does not specifically teach treatment or inhibition of growth of various tumors, it broadly teaches that taurolidine and/or taurultam may treat any type of tumor. Therefore it would have been obvious to a person of ordinary skill in the art at the time the invention was made to have modified Monson's teachings by branching off methods of treatment, prophylaxis and types of tumors such as glioblastoma and ovarian cancers.

Double Patenting

The **nonstatutory** double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA

1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims **1-8, 10-20 and 22-24** are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-19 of U.S. Patent No. 6,703,413. Although the conflicting claims are not identical, they are not patentably distinct from each other because claims **1-8, 10-20 and 22-24** are generic to all that is recited in claims 1-19 of U.S. Patent No. 6,703,413. That is, claims 1-19 of U.S. Patent No. 6,703,413 fall entirely within the scope of claims **1-8, 10-20 and 22-24** or, in other words, claims **1-8, 10-20 and 22-24** are anticipated by claims 1-19 of U.S. Patent No. 6,703,413. Specifically instant claims are drawn to a method of inhibiting growth of tumor cells or a method of killing a tumor cell comprising administering a composition comprising taurolidine, taurultam or a biologically active derivative thereof. These are the same limitations set forth in claims of U.S. Patent No. 6,703,413.

Claims **1-8, 10-20 and 22-24** are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-43 of U.S. Patent No. 6,995,164. Although the conflicting claims are not identical, they are not patentably distinct from each other because claims **1-8, 10-20 and 22-24** are generic to all that is recited in claims 1-43 of U.S. Patent No. 6,995,164. That is, claims 1-43 of

U.S. Patent No. 6,995,164 fall entirely within the scope of claims **1-8, 10-20 and 22-24** or, in other words, claims **1-8, 10-20 and 22-24** are anticipated by claims 1-43 of U.S. Patent No. 6,995,164. Specifically, instant claims are drawn to a method of inhibiting growth of tumor cells or a method of killing a tumor cell comprising administering a composition comprising taurolidine, taurultam or a biologically active derivative thereof. These are the same limitations set forth in claims of U.S. Patent No. 6,995,164.

Claims **1-8, 10-20 and 22-24** are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-20 of copending Application No. 11/350,313. Although the conflicting claims are not identical, they are not patentably distinct from each other because claims **1-8, 10-20 and 22-24** are generic to all that is recited in claims 1-20 of the copending application 11/350,313. In other words claims **1-8, 10-20 and 22-24** are anticipated by claims 1-20 of the copending application 11/350,313.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Response to Arguments

Applicant's arguments filed 01/05/07 have been fully considered but they are not persuasive.

Applicant argues against the combination of Pfirrmann et al and Morrissey and their application against the claims as amended. It is argued that the said references

"alone or in combination, do not disclose or suggest the use of taurolidine, tauraltum and/or a biological derivative thereof to inhibit the growth of a recurrent tumor". This is not persuasive because the references teach treating "tumors" which is interpreted as including recurrent and non-recurrent tumors. In other words the prior art does not distinguish between the recurrent and non-recurrent tumors and does not indicate a different method of treatment for recurrent tumors. In fact, the instant specification as well as prior art disclose the same treatment method for all tumors, including recurrent.

Applicant makes analogous argument against Monson and also with regards to the nonstatutory double patenting rejections. As mentioned above, there is no distinction made between treating recurrent tumors and other tumors, thus applicant's arguments are not found persuasive. The new rejection of claims over Stendel et al supports this argument even more as it is disclosed clearly that the said treatment (same treatment) is applicable for e.g. gliomas and recurrent gliomas.

No claim is allowable.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within

TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Mina Haghighatian whose telephone number is 571-272-0615. The examiner can normally be reached on core office hours.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Johann Richter can be reached on 571-272-0646. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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Patent Examiner
April 30, 2007

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